Decision Memo for Lung Volume Reduction Surgery (CAG-00115R)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) has made the following determinations regarding lung volume reduction surgery:

- The evidence is adequate to conclude that lung volume reduction surgery (LVRS) is not reasonable and necessary for high-risk patients with severe emphysema. A high-risk patient is one who has a forced expiratory volume in the first second (FEV_1) that is 20% or less of their predicted value and either homogeneous distribution of emphysema on CT scan or low carbon monoxide diffusing capacity (D_LCO) that is 20% or less of their predicted value. LVRS remains noncovered for this population group.

- The evidence is adequate to conclude that LVRS is reasonable and necessary for non-high risk patients who satisfy the inclusion and exclusion criteria outlined in the National Emphysema Treatment Trial (NETT) protocol and present with severe upper lobe emphysema.[1] Therefore, CMS intends to issue a national coverage determination covering LVRS for this indication.

- The evidence is adequate to conclude that LVRS is reasonable and necessary for non high-risk patients who satisfy the inclusion and exclusion criteria outlined in the NETT protocol and have severe non-upper lobe emphysema with low exercise capacity. Therefore, CMS intends to issue a national coverage determination covering LVRS for this indication.

- The evidence is adequate to conclude that LVRS is not reasonable and necessary for non high-risk patients who satisfy the inclusion and exclusion criteria outlined in the NETT protocol and have severe non-upper lobe emphysema with high exercise capacity. LVRS remains noncovered for this indication.

- All other patient indications for LVRS remain noncovered.

Covered LVRS approaches are limited to bilateral excision of damaged lung with stapling performed via median sternotomy or video-assisted thoracoscopic surgery.

In addition, CMS has determined that LVRS is reasonable and necessary only if preceded and followed by a program of diagnostic and therapeutic services consistent with those provided in the NETT and designed to maximize the patient's potential to successfully undergo and recover from surgery. The program must include a 6 to 10 week series of at least 16, and no more than 20, preoperative sessions each lasting a minimum of two hours. It must also include at least 6 and no more than 10 postoperative sessions each lasting a minimum of two hours, within 8 to 9 weeks of the LVRS. This program must be consistent with the care plan developed by the treating physician following performance of a comprehensive evaluation of the patient's medical, psychosocial and nutritional needs, be consistent with the pre-operative and post-operative services provided in the NETT, and arranged, monitored and performed under the coordination of the facility where the surgery takes place.

Finally, CMS has determined that LVRS is reasonable and necessary only when performed at facilities that were identified by the National Heart, Lung, and Blood Institute (NHLBI) as meeting the thresholds for participation in the NETT and at sites that have been approved by Medicare as lung transplant facilities. Currently, CMS is developing accreditation standards for sites that perform LVRS and, when implemented, LVRS will be considered reasonable and necessary only at accredited facilities.

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Decision Memo

TO: Administrative File: CAG - 00115R
Lung Volume Reduction Surgery (LVRS)

FROM:

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SUBJECT: Coverage Decision Memorandum for Lung Volume Reduction Surgery
DATE: August 20, 2003

I. Decision

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II. Background

Pulmonary emphysema is a common, progressive, disabling disease with a high mortality rate. Emphysema is a condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by destruction of alveolar walls and resulting in the chronic hyperinflation of the lung. This destruction of the alveolar-capillary membrane leads to a reduction in the surface area available for gas exchange and a loss of elastic recoil of the lung. As the disease progresses, the area of gas exchange decreases and patients become progressively short of breath and limited in activity. Advanced emphysema patients struggle for breath when they perform simple tasks such as climbing stairs or carrying groceries. Emphysema is usually the result of cigarette smoking, although it is less frequently associated with inhalation of coal dust and can also occur in a genetic condition known as alpha 1 antitrypsin deficiency.

In 1996, almost 2 million people in the United States suffered from emphysema. The prevalence of emphysema is highest in the over-65 age group where it is 32.4 per 1,000 compared to 6.9 per 1,000 in the general population. Race, socioeconomic status and geography also influence the prevalence of emphysema with the highest rates among the lower income white population in the mid-west of the US. Death rates due to emphysema increase markedly for those over 65 years of age. In 1999, approximately 18,000 people died from the disease, making emphysema a major cause of death among the elderly in this country. [2] [3]

Medical therapy. The goals of medical therapy for emphysema are to delay the progressive decline in lung function, prevent exacerbations of the disease, prolong survival and improve exercise capacity and quality of life. To date, smoking cessation and long-term oxygen therapy for certain patient groups are the only non-surgical treatments that have demonstrated survival benefit. Immunizations can sometimes prevent or reduce exacerbations caused by infections. Exacerbations are treated with a variety of antibiotics, anti-inflammatory drugs, and bronchodilators. Exercise conditioning and educational, psychosocial and nutritional services provided in pulmonary rehabilitation programs may improve exercise capacity and reduce disability.

Surgical approaches. Over the years, the limited success of medical therapy resulted in the development of numerous surgical procedures for different parts of the respiratory system in an attempt to alleviate symptoms and improve health outcomes. Although patients with severe emphysema have lungs that have become too large relative to the size of their chests, none of the operative procedures for the chest wall, diaphragm, pleura or nervous system to modify this condition have been shown to have lasting benefit.

Lung volume reduction surgery (LVRS) was first reported in 1957 as an attempt to reduce pulmonary hyperinflation by removing overdistended and presumably nonfunctional areas of the lungs. A high operative mortality rate and lack of observable measurements to substantiate the reported patient improvement limited acceptance of the procedure and led to its abandonment. Subsequently, in the early 1990s, a variety of modifications in technique were introduced to retest the hypothesis that reduction in lung volume would restore the elastic recoil of the lungs, open the small airways, and improve ventilatory mechanics. In 1995, the apparent improvement in lung function with wedge resection of emphysematous lung tissue reported in uncontrolled case series studies prompted a surge in utilization of this surgical procedure.[4]

In the 1990's version of the LVRS procedure, the resection of emphysematous lung was done by either a median sternotomy (MS), which involves an incision through the breastbone to expose the lungs, or by video-assisted thoracoscopic surgery (VATS). Thoracoscopy is a less invasive procedure that requires three small incisions between the patient's ribs and uses a video-scope to guide the surgeon. In both procedures the damaged lung tissue is cut away and the edge of the remaining organ tissue is stapled back together.

As with any surgical procedure, there are risks and complications involved in LVRS. The most common complication is post-surgical air leakage through the stapled lung tissue. Chest tubes are placed to monitor this complication and prevent the collapse of the lung. Additional complications include pneumonia, infection, stroke, bleeding, myocardial infarction, and death.

III. History of Medicare Coverage

In the mid 1990s, LVRS diffused rapidly in clinical practice despite a paucity of clinical evidence concerning its safety and effectiveness. Prior to December 1995, Medicare coverage of LVRS was left to contractor discretion – there was no national policy on the procedure. A September 1995 workshop sponsored by the NHLBI had called for controlled studies of the surgical approach. In December 1995, CMS (then HCFA) issued a national noncoverage policy for all LVRS procedures based on the inadequacy of medical evidence and the potential for extensive morbidity and mortality among Medicare beneficiaries given its rapid diffusion.[5]

One of the most important shortcomings of the literature at the time was the high percentage of treated patients who were lost to follow-up in the post-surgical period and the failure to assess their outcomes. The loss of patient data was most notable beyond 3 months post-surgery. As a result the validity of subsequent reported outcomes could not be ascertained since they could have been subject to considerable bias depending on whether the patients that maintained contact with providers had predominantly positive or negative results. Uncertainty about the post-operative survival rates for LVRS was a particular concern for CMS given the rapid dissemination of the intervention beyond the academic centers originally reporting results in the medical literature. To address this concern, a specific ICD-9 code was assigned to the procedure and CMS performed an analysis of Medicare claims between October 1995 and January 1996. The agency identified 722 claims for LVRS during this period and found that approximately 30% (N=215) of the Medicare beneficiaries had died within 18 months of their surgery – a mortality rate much higher than that reported or projected in published studies.

In April 1996, the Agency for Healthcare Research and Quality (AHRQ, then the Agency for Health Care Policy and Research,) issued a pre-publication copy of a report requested by CMS on the available evidence on LVRS. The technology assessment found that the available evidence did not permit scientific conclusions regarding risks and benefits of LVRS.[6] Because some patients appeared to benefit in the short run, AHRQ recommended that Medicare coverage be provided within a controlled clinical study.

Later that month, CMS and NHLBI concluded that data from controlled clinical trials were needed to reliably guide the appropriate use of LVRS and signed an agreement to participate in such study. As part of this memorandum of understanding, NHLBI would design and fund the clinical trial and CMS would reimburse for the health care services provided to beneficiaries treated under its protocol. Surgery outside the protocol of the NETT would not be covered under the Medicare program. Beneficiaries would be provided access to a promising but not yet proven procedure while scientifically valid data were generated to guide future clinical use and reimbursement decisions. Thus, the two agencies, in concert with a number of academic investigators skilled in the performance of the procedure, developed the National Emphysema Treatment Trial (NETT). The NETT became a multicenter, randomized clinical trial of medical therapy vs. medical therapy plus LVRS in the treatment of emphysema. Data resulting from the trial published in May 2003 provided the basis for this coverage determination.

IV. Timeline of Recent Activities

December 1995	CMS (then HCFA) issues a national non-coverage policy on LVRS procedures
April 1996	CMS and NHLBI sign an agreement to sponsor a controlled clinical trial on LVRS
October 1997	Patient screening for the NETT begins
October 2001	NETT investigators publish a finding from the trial describing a subpopulation of severely ill patients for whom surgery increases the risk of death.
July 2002	Patient enrollment for the NETT ends
August 2002	Investigators perform last surgery under the trial protocol
October 2002	CMS begins discussion of trial data with NETT investigators
May 2003	NETT investigators publish report on primary outcomes for all study patients.
May 20, 2003	CMS opens a national coverage determination (NCD) on LVRS

V. FDA Status

Lung volume reduction surgery is a procedure that does not require FDA approval.

VI. General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. The goal of our determination process is to assess net health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

An intervention is not reasonable and necessary if its risks outweigh its benefits. For all determinations, CMS evaluates whether reported benefits translate into improved net health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

4. Specific LVRS Methodological Principles

Certain principles of study design are particularly relevant in the evaluation of the evidence available on LVRS. Methodological principles designed to limit bias and increase the validity of the results were not always fully observed in the individual studies on LVRS reported before the NETT was initiated. These key methodological requirements are briefly discussed below and include the need for a comparison group (particularly when the natural history of the condition in the population of interest is not well known), random assignment of patients to experimental and control groups, limiting attrition in both study groups, following up subjects for an adequate length of time, taking confounding variables into account, and analyzing results according to patients' original group assignment.[7]

An issue of particular concern regarding the evidence available on LVRS prior to the initiation of the NETT trial was the absence of published prospective controlled trials (either randomized or non-randomized) comparing optimal medical therapy plus LVRS with optimal medical therapy alone. The clinical evidence available prior to 2000 came almost exclusively from case-series.

While never as definitive as controlled studies, the value of case series can be increased when there is a detailed knowledge of the natural history of the disease for a population of interest, to serve as a reference point. Such detailed knowledge was not available for the population of patients with severe emphysema for whom LVRS was indicated. Epidemiological studies including emphysema patients had been based on data collected from populations of patients with chronic obstructive pulmonary disease (COPD) rather than patients with emphysema as their exclusive pulmonary disorder. Thus, given the lack of a comparable population for which LVRS would be indicated, evidence from case-series was not adequate to conclude that LVRS was safer or more effective than optimal medical treatment.

One of the most important shortcomings of the LVRS literature was excessive attrition (i.e., a high percentage of treated patients were lost to follow up in the post-surgical period) raising the concern that reported outcomes for patients available for follow up were not representative of the group as a whole. Poor follow-up is seldom random and patients with better outcomes are usually over-represented. In the case of LVRS, it is likely that death occurs most commonly in those patients with a poor result after surgery and that subsequent data are measured only in those patients who are more robust or who have benefited from surgery.[8] All LVRS prospective studies reported prior to the NETT were affected by attrition ranging from 3% to 55% depending on follow-up time considered. [9]

Unless studies follow patients beyond the first couple of months after a major therapeutic intervention, experience with the durability of reported benefits will remain uncertain. Given the potentially significant morbidity and mortality risks from a procedure such as LVRS, more than a transient improvement in health outcomes is necessary to offset the risk of surgery. It is important to have a substantial length of follow-up to capture the totality of the expected risks and benefits attributed to the procedure. Whereas none of the prior studies reported data beyond 12 months from surgery, the NETT investigators set out to report and published results on outcomes of interest up to at least two years after surgery.

One of the most important aspects of clinical research is the inference that an association represents a cause-effect relation (in this case between LVRS and improved health outcomes). Services provided in pulmonary rehabilitation programs have been shown to have an effect on exercise capacity and quality of life in patients with COPD.[10] A confounding variable such as pulmonary rehabilitation may be associated with the surgical intervention and be in fact the cause of the outcome observed. One of the persistent questions unanswered by research prior to the NETT has been the impact of pulmonary rehabilitation services on outcomes observed from LVRS. To the extent that studies did not consistently include and document the use of comparable pulmonary rehabilitation services in both experimental and control groups, it was difficult to determine if the outcomes were the result of the surgical procedure or an effect of exercise conditioning, psychosocial interventions, or other rehabilitation services.

Finally, most of the LVRS trials prior to the NETT were survivors-only analysis rather than the preferable intention-to-treat analysis. Differential early mortality due to surgery could make LVRS survivors appear healthier by removing weaker patients from follow-up. A survivors-only analysis could distort the interpretation of outcomes such as pulmonary function, exercise capacity, and quality of life.

VII. Evidence

A. Introduction

Consistent findings across studies of net health outcomes associated with an intervention as well as the magnitude of its risks and benefits are key to the coverage decision process. For this decision memorandum, CMS reviewed the published clinical evidence on LVRS since the publication in September 1996 of the above-mentioned AHRQ technology assessment (TA) report to determine whether optimal medical management plus LVRS in comparison with optimal medical management alone improves the net health outcomes of patients with severe emphysema.

A number of systematic reviews on LVRS summarizing and critically appraising the literature on the topic have covered studies published during this period through September 2001. CMS performed a search for additional, more recently published relevant articles to supplement these systematic reviews. This literature search was limited to comparative prospective studies including randomized and non-randomized controlled clinical trials. Prominent among the studies providing new evidence were two articles reporting clinical results from the NETT, which is the largest randomized clinical trial on the subject to date. In addition to our review of the clinical scientific literature, we requested information from experts and professional societies and sought available evidence-based practice guidelines, consensus statements, and position papers.

Outcomes of interest were the beneficial or adverse clinical effects of LVRS: mortality, improvement in maximum exercise capacity, patient-reported quality of life, respiratory symptoms, and pulmonary function. Mortality measures over time and the durability of the other outcomes (e.g., at 12 and 24 months) were of particular interest as were the characteristics of patients most likely to benefit or be at risk for the procedure.

Clinical investigators have utilized a variety of validated instruments and tests to measure outcomes other than survival for patients with pulmonary disease. Measures of exercise capacity include maximal, incremental, symptom-limited cycle ergometry (e.g., using a cycle ergometer with five or 10 watt/minute ramp on 30% oxygen, after three minutes of unloaded pedaling) and the 6-min walk test.

General quality of life measures include the Medical Outcomes Study Short Form 36-item (MOS SF-36) questionnaire and the utility-weighted Quality of Well-Being Scale (QWB). The St. George's Respiratory Questionnaire (SGRQ) is an instrument validated in patients with COPD that assesses disease-specific quality of life. An instrument frequently used to measure dyspnea, the most important symptom of chronic lung disease, is the University of California at San Diego Shortness of Breath Questionnaire (SOBQ). The MOS SF-36, QWB, SGRQ, SOBQ are self-administered scales. Forced expiratory volume in one second (FEV1), forced vital capacity, total lung capacity and residual volume are among the pulmonary function tests typically utilized in clinical trials of LVRS.

B. Summary of evidence reviewed

1. Assessment questions

The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all requests: “Is the evidence sufficient to conclude that the application of the technology under study will improve final health outcomes for Medicare patients?” The formulation of specific questions for the assessment recognizes that the effect of an intervention can depend substantially on how it is delivered, to whom it is applied, the alternatives with which it is being compared, and the delivery setting. In order to appraise the net health outcomes of LVRS in comparison with medical therapy alone and identify relevant patient and facility selection criteria, CMS sought to address the following questions:

- Does LVRS with medical therapy improve health outcomes in Medicare patients with severe emphysema compared to medical therapy alone?
- What subgroups of patients with severe emphysema are likely to benefit from the procedure?
- Should the performance of LVRS be limited to specific facilities?

2. External systematic reviews/technology assessments

Systematic reviews are based on a comprehensive and unbiased search of published studies to answer a clearly defined and specific clinical question such as that related to the effectiveness of LVRS. A well-defined strategy or protocol (established before the results of the individual studies are known) guides this literature search. Thus, the process of identifying studies for potential inclusion and the sources for finding such articles is explicitly documented at the start of the review. Finally, systematic reviews provide a detailed assessment of the studies included.[11]

Three systematic reviews on LVRS that met these criteria were available to CMS at the start of this literature evaluation.[12] The following are summaries of these reports, which evaluated the clinical literature on LVRS published through September 2001.

a) Blue Cross and Blue Shield Association TA on LVRS for Severe Emphysema.[13]

This technology assessment reviewed the evidence available through March 1999 to determine whether optimal medical management plus LVRS in comparison with optimal medical management alone improved health outcomes for patients with severe emphysema. The TA reviewed the outcomes of LVRS performed by bilateral staple excision via median sternotomy (MS) and via video-assisted thoracoscopy (VATS) but did not review unilateral or laser approaches to LVRS.

The health outcomes of interest were increased exercise tolerance, symptom reduction and improved quality of life. Intermediate outcomes were pulmonary function tests (which included FEV1, forced vital capacity, total lung capacity and residual volume). The harmful health outcomes of interest were procedure-related morbidity and mortality.

In the absence of completed randomized clinical trials, reports of original data that specified patient selection criteria, treatment performed, and outcome measures were selected for review. Fourteen articles of the 32 reports selected for detailed review were included in the analysis of evidence. Eleven articles contained primary evidence and 3 additional papers included data on various subsets of a patient cohort described in one of the original articles.

The 14 studies reported data for at least 475 patients undergoing LVRS performed by bilateral staple excision and followed patients anywhere from one to 36 months. The primary evidence consisted of 11 uncontrolled case series. One of the 3 supplemental reports was a retrospective case-controlled study that compared 65 LVRS recipients to 22 LVRS candidates who did not receive the operation.

Results

Morbidity and mortality: Pooling all morbidity data resulted in morbidity outcomes on 466 procedures. Prolonged air leak was the most common adverse event occurring in 40.6% of cases. Other frequent complications included pneumonia (8.8% incidence) and cardiovascular events (8.4% incidence). Reoperations were necessary in 19 cases (4.1% incidence). Twelve studies provided information on operative mortality. In studies of 30 patients or less, the operative death rate ranged from zero to 20%. The three largest series (involving 120 to 150 patients) reported operative mortality of 4 to 5%. The pooled operative mortality rate for 759 procedures was 4.1% and involved 31 deaths. Operative mortality was defined and reported variably (e.g., 30-day vs. 90-day definition).

Exercise capacity outcomes measured by the 6-minute walk were reported in six studies. Each of these reports described short-term improvement in 6-minute walk distance measured one to six months after surgery. Longer-term data were reported for small subgroups at 12, 24 and 36 months post-surgery. For instance, for a subgroup of 56 patients, the walk distance had improved from 1150 feet at baseline to 1362 feet at six months, and 1357 feet at 12 months after surgery. Some studies reported improved work capacity measured in watts by bicycle ergometer testing. Preoperative and postoperative pulmonary rehabilitation protocols were variably reported.

Quality of life outcomes were measured directly in a small minority of studies. The quality of information was also limited by the number and type of instruments utilized. For instance, two studies reported results of a single question (i.e., how patients viewed their overall health status compared with one year earlier). In the first study, the great majority (78%) of the 108 patients evaluated at six months (out of 127 eligible) responded “much better” and an additional 20% responded “somewhat better.” The second study reported similar results based on 17 of 26 patients available at the 3-month evaluation. Another study compared baseline and three-month scores on the St. George Respiratory Questionnaire in a small patient sample (11 of 14) and noted that mean total score had improved from 62 at baseline to 31 at 3 months post-operatively.

Respiratory symptoms. Five studies used the Modified Medical Research Council (MMRC) dyspnea scale to measure the effect of LVRS on symptom change and reported improved scores up to three months post-operatively. Baseline MMRC scores were reported for 304 patients. Although improved for those reported, scores were only available for 218 patients at six months and for 17 patients at 12 months after surgery. Some studies also reported improvement in dyspnea symptoms for a subgroup of patients at three, six and twelve months after surgery as measured by other scales such as the Mahler Baseline Dyspnea Index (BDI) and Transitional Dyspnea Index (TDI).

Pulmonary function measures. All papers reviewed consistently reported short-term improvements in pulmonary function variables including FEV1, forced vital capacity, total lung capacity and residual volume. Eight studies reported improvements in FEV1 measured during the first three months post-surgery. There were few data available to assess the durability of FEV1 change beyond six months.

Appraisal

Citing the following limitations of the available evidence, the BCBS report found the scientific evidence inadequate to permit conclusions concerning the effect of LVRS on health outcomes.

The published articles presented case series data rather than evidence from well-designed and controlled clinical studies. Whether LVRS favorably or adversely affected morbidity and mortality rates relative to what would be experienced by end-stage emphysema patients in the absence of surgery could not be assessed adequately using the available data because of the absence of a comparison group or a good natural history for the group of patients selected. In addition, the inconsistent use and reporting of pre- and postoperative rehabilitation confounded the assessment of LVRS outcomes making it difficult to determine if the outcomes were the result of the surgical procedure or an effect of rehabilitation.

The principal health outcomes of interest were measured inadequately in the articles reviewed. For instance, although a major objective of LVRS is to improve the patient's quality of life, only three of 11 studies included data on quality of life and each used a different instrument to assess the outcome. Although, all available studies reported improvements in pulmonary function tests, these tests were not adequate surrogates for functional outcomes or quality of life.

A high percentage of treated patients were lost to postoperative follow-up. The missing data created the potential for strong biases in the reported results. The morbidity and mortality risks associated with LVRS can be substantial. Given the potential complications, more than a transient improvement in health outcomes is necessary to offset the risks of surgery. In addition, experience with the durability of reported benefits remained uncertain based on studies reviewed. Although baseline data was reported for 506 operated patients, only 56 patients had 12 month outcomes, 20 patients had 24 month outcomes and 18 patients had 36 month outcomes for some variables.

The report concluded that better data on longer-term health outcomes were needed to determine the risk/benefit balance of LVRS. Additionally, the report asserted the need for a randomized controlled trial with long-term postoperative follow-up to determine the effect of LVRS on health outcomes and expressed support of the NETT trial then in progress.

b) LVRS for COPD with Underlying Severe Emphysema.[14]

Young et al. published a systematic review of the literature on LVRS in September 1999 on the evidence of the effects of LVRS in patients with end stage COPD secondary to severe emphysema. Outcomes of interest included mortality, exercise capacity measured by the six minute walking distance, quality of life, dyspnea and lung function tests. The authors found that the most rigorous evidence on the effectiveness of LVRS came only from case series.

Results

The pattern of results across the 19 case series that met criteria for inclusion was consistent across individual studies. Statistically significant short-term benefits occurred across a range of outcomes. The authors re-calculated data when necessary and used additional statistics such as the interquartile range (IQR) to indicate the general size and direction of effect across studies.

Mortality: Early and late mortality rates could be calculated for most series accounting for a total of 567 patients. The interquartile range (IQR) for early mortality (defined as hospital deaths or deaths occurring within 30 days of surgery) was 0-6% while the IQR for late mortality (deaths occurring in the home or more than 30 days after surgery) at 3-6 months was 0-8%.

Exercise capacity: Ten studies collected data on this outcome for 486 patients performing the 6-minute walk test. The reviewers converted all results to meters to facilitate comparison. The baseline distance covered by study participants was 241-290 m (IQR). This rose to 306-434 m after treatment with a pre/post difference of 32-96 m. Only one study recorded these data in the longer term with differences of 64 m and 80 m at one and two years respectively.

Quality of life: Only four series collected quality of life data before and after the procedure (187 patients) and only three of these used specific measurement tools. Different instruments were utilized in each of these studies (including the Chronic Respiratory Disease Questionnaire, the MOS SF36, the Nottingham Health Profile, and the Sickness Impact Profile.) Although limited data were presented, improvements in quality of life were observed across all studies and measurement tools.

Respiratory symptoms: Twelve studies measured dyspnea before and after the intervention utilizing a variety of measurement tools. Only nine studies used validated standardized tools. The most commonly used instrument was the modified (American Thoracic Society) Medical Research Council of Great Britain scale (MMRC). Results were reported for 403 patients and showing improvement across studies with mean pre-post differences of 1.0 to 2.4 in dyspnea scale scores. Scales used in other studies included the Mahler baseline dyspnea index (BDI), the transitional dyspnea index (TDI) and the Borg scale.

Pulmonary function measures: Most studies collected data on a range of physiological outcomes including the forced expiratory volume in one second (FEV1). FEV1 data were available for 925 patients. At baseline the FEV1 was 0.64-0.73 liters (IQR) which rose to 0.91 -1.07 liters at 3-6 months after LVRS with a pre/post difference of 0.23-0.36 liters.

Appraisal

The authors noted that the available evidence appeared to support the effectiveness of LVRS but that the studies reviewed employed designs that made them susceptible to bias. The entire research base for the intervention at the time of the review was subject to the limitations of study designs without parallel control groups. Although studies provided outcome measures before and after an intervention, the attribution of all or any observed change to LVRS was uncertain. Particularly important was the role of pulmonary rehabilitation as a factor influencing the difference between the pre and post-treatment outcome measurements since the LVRS “package” would have likely included preoperative pulmonary rehabilitation in a number of studies. Without a parallel control group it was not possible to exclude the possibility that rehabilitation alone might have caused a considerable component of the improvement in outcomes of interest such as exercise capacity, quality of life and dyspnea.

The possibility of detection bias was another concern for reviewers. With only one study arm, clinicians and patients were aware that they were on an active treatment and might have inadvertently provided outcome information that conformed to their expectations that LVRS would result in improvement. Therefore, although LVRS appeared to represent a promising option in the management of patients with severe end stage emphysema, the authors concluded that the considerable uncertainty that existed around the effectiveness of the procedure would remain until the results of randomized controlled clinical trials became available.

c) ECRI (Emergency Care Research Institute) Technology Assessment Report: LVRS for emphysema.[15]

Since the publication of these reviews calling for controlled studies, a number of randomized and non-randomized controlled trials have been conducted. ECRI published a report in September 2001 that summarized and analyzed newly available data from such studies.

The ECRI report addressed a variety of questions pertaining to LVRS and its effectiveness in the palliative treatment of emphysema based on the findings of clinical trials reported in the published, peer-reviewed literature. In particular, the report addressed whether LVRS was an effective palliative treatment option for emphysema when compared to optimal medical therapy. To address this question, the authors identified morbidity and mortality, exercise tolerance, quality of life, dyspnea symptomatology and pulmonary function (including measures of blood gases) as the outcomes of interest.

The authors systematically searched databases including the Cochrane Database of Systematic Reviews, the Cochrane Library and Registry of Clinical Trials, Embase, HealthSTAR, Medline and others. The search strategy employed free text key words and controlled vocabulary terms including “randomized controlled trials,” “controlled clinical trials,” “emphysema,” “pneumonectomy,” “lung/surgery,” “lung volume reduction” and “LVRS”. Hand searches of journal and non-journal literature were used to retrieve additional relevant information.

A two-tiered approach was adopted to determine which studies to include in the technology assessment. A first set of criteria guided what articles identified by the search would be retrieved:

- The study concerned the treatment of emphysema with LVRS and provided data addressing the assessment question.
- The study was reported in the English-language peer-reviewed literature.
- The study must have utilized a suitable control or comparison (concurrent, contemporaneous, or historical) group.
- The study must have included at least ten patients in each arm, and
- The study could be retrospective if patients were selected consecutively.

Criteria specific to the assessment question were subsequently applied:

- Study was reported as full article rather than as abstract.
- Study must have compared the effectiveness of LVRS directly with standard medical management in a comparable group of patients (concurrent or historical control group).
- Study patients had diffuse severe emphysema and significant functional limitation despite optimal medical therapy.

- LVRS techniques included were unilateral or bilateral median sternotomy or VATS using stapling, and
- Only the largest report from the same center was assessed.

Results

The authors found five controlled trials meeting these inclusion criteria to address the assessment question. Three of the five studies were prospective, randomized controlled trials.[16] Of the two non-randomized controlled studies only one was prospective.[17] The authors conducted meta-analyses of the studies reviewed whenever they considered it possible to calculate summary estimates of effect size for the required outcomes. (Details of the prospective studies and the characteristics of the patients enrolled in them are included in the evidence table in the appendix for purposes of comparison with more recent prospective controlled studies such as the NETT reports.)

Perioperative morbidity. Only one of the five studies presented data on this measure of outcome. Air leaks were the predominant cause of postoperative morbidity affecting 50% to 60% of patients, followed by pneumonia (7% to 5%). Less frequently reported hospital complications were bleeding, ventilator dependence, and tracheostomy.

Mortality. Inconsistencies in the summary findings of the meta-analyses precluded the authors from drawing conclusions regarding any difference between the experimental and control groups in short-term (<30 days) or long-term mortality (follow-up time ranging from 3 to 48 months in among studies).

Exercise capacity. All four prospective studies reviewed presented data related to exercise tolerance (three used the six-minute walk test and the fourth used a “shuttle-walking test”). Meta-analysis of the data showed that patients who received LVRS demonstrated better tolerance to exercise at follow-up (time interval range between 3 and 24 months) than their counterparts in the medical group. This finding was robust and was not overturned by adjustments for attrition.

Quality of life. Only one of the studies reported quality of life measures for both arms. Geddes et al. (2000) found that quality of life measured by Medical Outcomes Study Short Form 36-item (MOS SF-36) scores improved in patients who received LVRS and declined in those who received medical therapy. There was no statistically significant difference in between-group scores at three months post-surgery but one emerged at six-month and 12-month follow-ups.

Respiratory symptoms. Two studies reported data on this measure. Pompeo et al. (2000) showed that patient-reported dyspnea was reduced at 24 months in both arms among patients who completed the study, with the greatest reduction in symptoms seen in the LVRS arm. Wilkens et al. (2000) also found that post-treatment mean dyspnea scores showed more improvement in the treatment group at various follow up assessments but high attrition (up to 55%) severely weakened these findings.

Pulmonary function measures. FEV1 has been considered by investigators in the field to be the primary outcome measure of interest. FEV1 was the only of these surrogate measures reported in all studies reviewed. The authors confined their meta-analysis of pulmonary function data to this outcome and found that patients who were treated with LVRS benefited from treatment more with respect to FEV1 than those who were treated by optimal medical therapy alone. The few studies reporting on blood gas measures showed no conclusive evidence that LVRS improved PaO2, PaCO2, or carbon monoxide diffusing capacity (DLco) compared to medical treatment.

Appraisal

Based on quantitative analyses of data extracted from three randomized controlled trials and two non-randomized controlled trials, the authors found that the evidence suggested that LVRS improved pulmonary function and exercise tolerance but noted limitations of the evidence base.

The authors acknowledged that non-randomized allocation to treatment or control group might lead to substantial selection bias. Two non-randomized controlled studies were nevertheless included in the TA analyses. In the prospective study by Wilkens et al. (2000), patients who requested LVRS were assigned to the treatment group; those who agreed to postpone surgery for at least a year formed the control group. In this instance, it was difficult to determine whether any effect of treatment was the result of the procedure or an artifact due to between-group differences in motivation or other variables. The retrospective study by Meyers et al. (1998) compared a group of patients who had received LVRS with a chosen group of patients who had been evaluated and approved for the procedure but did not receive it due to lack of insurance coverage.[18] The TA authors noted they were unable to confirm that the latter study with “contemporaneous” controls was free from selection bias due to lack of reported data. Some methodologists consider non-randomized studies inadequate because the causal relationship between the treatment and outcome cannot be established with any certainty.

In four of the five studies, approximately 25% of those patients who were screened as possible candidates for LVRS met similar inclusion criteria for entry. As a consequence, the results of the studies could be generalizable to only a small subset of patients with emphysema.

All four of the prospective studies were affected by attrition ranging from 3% to 55% depending on follow-up time. In addition, none of these studies carried out an intent-to-treat analysis. High attrition rates may bias interpretation of data that are collected in longitudinal studies. Missing data affect the validity of a study in two ways. First, the loss of data reduces the statistical power of the study. Second, attrition can create a bias when patients who drop out are different from those who remain in the study.

Although results from single studies suggested that LVRS improved quality of life and dyspnea symptoms when compared to optimal medical therapy alone in a select group of patients with severe emphysema, this evidence was weak since the relevant data were scarce. When taken together, the analysis of the evidence suggested that LVRS did have a palliative effect when compared to medical therapy but the available evidence base was inadequate given the short follow up to draw strong conclusions about the long-term effectiveness (>12 months) of the procedure.

The authors of the ECRI report could not come to evidence-based conclusions about morbidity and survival. They noted inconsistencies in the data, concluding those inconsistencies would be resolved only by more data coming from prospective (preferably randomized,) controlled trials that carefully report short-term and long-term mortality data.

3. Internal technology assessment

CMS staff also performed a search of any individual LVRS effectiveness studies available since the publication of the above-mentioned systematic reviews, which summarized the literature on the procedure through September 2001. We defined the following inclusion and exclusion criteria for the selection of additional articles published since then.

Literature search strategy

- Studies would be comparative and prospective but not necessarily limited to randomized controlled trials
- Case series and case reports would be excluded
- Studies would include persons of any sex, ethnic origin, and age that received LVRS
- Procedures would be limited to bilateral staple excision via median sternotomy or via video-assisted thoracoscopy (unilateral or laser techniques excluded)
- Studies would be conducted in an inpatient setting and reported in English.

Although observational studies had suggested that LVRS might be effective, stronger evidence currently exists from which to draw conclusions about its effectiveness. CMS staff thus limited the search to prospective controlled clinical trials with publication years 2001 through 2003.[19] We used the following electronic search strategy of the Medline database for this period.

- Emphysema AND (emphysema surgery OR lung volume reduction surgery OR LVRS OR volume reduction surgery OR pneumectomy OR reduction pneumoplasty OR lung reduction surgery)

Abstracts of the references were reviewed for inclusion. We sought to identify any additional relevant articles through manual search of references and communications with researchers in the field. We screened the full-text of retrieved articles to determine whether they met the inclusion criteria for the review and extracted data from eligible studies.

Search results

In addition to the three systematic reviews, the literature search yielded 33 articles for abstract review. Five articles met the inclusion criteria. Four of these studies had been included in the ECRI TA report summarized above. The first report on the NETT was the only additional article subsequently published meeting the search criteria that we were able to identify. In the course of the review, CMS also evaluated the manuscript reporting on NETT results for non-high risk patients at the time it was submitted for publication. Key data from these six articles reporting on controlled prospective trials (including both NETT reports now published) appear in evidence tables in the Appendix. The information contained in these tables serves as the basis for CMS conclusions about the overall adequacy of the evidence in determining whether LVRS should be considered reasonable and necessary. Below is a detailed summary and appraisal of the findings produced by the two NETT studies recently added to the literature.

The National Emphysema Treatment Trial (NETT) [20]

The NETT was a multicenter, randomized unmasked clinical trial of medical therapy vs. medical therapy plus LVRS for the treatment of patients with severe bilateral emphysema. NHLBI and CMS cosponsored this trial to provide information on the role of LVRS in the management of emphysema, define the characteristics of patients who were likely to benefit from or be adversely affected by the procedure, and serve as a basis for a CMS decision on coverage for LVRS.

As mentioned above, NHLBI and CMS had concluded that such a trial was needed since the effects on mortality, the magnitude and durability of benefits, and patient selection criteria for this palliative procedure for severe emphysema had not been well established at the time the trial was conceived. Key questions unanswered by the literature available were:

- How long will the benefit from surgery last?
- What is the optimal technique for performing the procedure?
- What are the clinical outcomes beyond the first few months after surgery?
- Can a subset of patients who will benefit from the procedure be defined?

Study design and methods

Screening began in October 1997 following finalization of the NETT protocol and procedures. The NETT investigators published a special report in the peer-reviewed literature describing the rationale and design of the trial once the NETT was underway. [21]

The two primary outcome measures chosen were survival and maximum exercise capacity two years after randomization. Investigators chose mortality as a primary outcome measure since a statistical design for differences in survival would ensure a sufficient number of participants for important outcome measures related to palliation (measured by exercise capacity, quality of life and dyspnea scores). Investigators chose maximal, incremental, symptom-limited exercise capacity using a cycle ergometer as the measure of maximum exercise capacity (i.e., cycle ergometry with five or 10 watt/minute ramp on 30% oxygen, after three minutes unloaded pedaling). Advantages cited for this test over the 6-min walk test were ease of administration, better standardization, reproducibility and less learning effect.[22] Investigators favored exercise capacity over pulmonary function tests as a primary measure of outcome because previous studies had not documented a consistent relationship between changes in pulmonary function and improvements in functional status (e.g., dyspnea, quality of life).

Secondary outcomes included general quality of life as measured by the MOS SF-36 questionnaire and utility-weighted Quality of Well-Being Scale (QWB). Disease-specific quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ), an instrument that had been validated in patients with COPD. The University of California, San Diego Shortness of Breath Questionnaire (SOBQ), and the modified Borg scale for perceived dyspnea were used to assess dyspnea, the most important symptom of chronic lung disease. The SF-36, QWB, SGRQ, SOBQ are self-administered scales. The modified Borg scale was also used at the start and close of exercise testing to obtain ratings of dyspnea and muscle fatigue before and after exercise.

Pulmonary function and gas exchange were assessed in all patients at the time of the initial evaluation and at all follow-up visits. Tests included FEV1 percent predicted, total lung capacity, residual volume, carbon monoxide diffusing capacity (percent predicted). Arterial blood gas measurements included PCO2 (mm Hg) and PO2 (mm Hg).

The severity and distribution of emphysema were determined from chest high-resolution computed tomographic (HRCT) scans at the time of initial evaluation and at two follow-up visits to assess the distribution and severity of the disease. Other measures included echocardiography to evaluate right ventricular function (e.g., rule out pulmonary hypertension) performed at initial assessment and at one follow-up visit. The Trail Making Test at baseline and annual follow-up visits was used to evaluate changes in cognitive ability over time (i.e., attention and psychomotor functioning). Finally, cost effectiveness analyses were also performed using incremental quality-adjusted life years or QALYs to incorporate total value gained for resources expended (i.e., incremental costs) yielding cost-effectiveness estimates expressed in dollars per QALY gained.

The main protocol involved all enrolled patients at all participating clinical centers and addressed the primary and secondary objectives of the NETT. Several substudies addressing specific issues were performed at selected centers and involved only patients enrolled in those centers. The study duration was set at 4.5 years with a 6-month closeout period.

Patients with moderate to severe emphysema who had been nonsmokers for six months prior to randomization and were judged to be free of other diseases or circumstances likely to interfere with therapy or data collection for the duration of the trial were eligible for enrollment in the NETT. In addition to recruiting patients likely to be able to complete the trial, the patient selection criteria were formulated to achieve two other broad goals: enrollment of patients with either heterogeneous or homogeneous emphysema and exclusion of patients at high risk for perioperative morbidity or mortality.

Specifically, inclusion criteria comprised radiographic evidence of moderate to severe bilateral emphysema, demonstrated severe airflow obstruction and hyperinflation of the lung (e.g., FEV1 at or below 45% of predicted) and participation in pulmonary rehabilitation with the attainment of preset performance goals (e.g., ability to complete three minute unloaded pedaling in an exercise tolerance test). Exclusion criteria included previous lung surgery, COPD conditions unsuitable for LVRS (e.g., bronchiectasis, chronic bronchitis, and CT evidence of diffuse emphysema judged unsuitable), cardiovascular disease, and evidence of systemic disease or neoplasias expected to compromise survival during the five-year period and unwillingness or inability to complete baseline data collection procedures.

Eligible patients participated in a supervised pulmonary rehabilitation program for 6 to 10 weeks prior to surgery. The purpose of pulmonary rehabilitation for medical therapy patients was to optimize exercise capacity. LVRS patients underwent rehabilitation to achieve physical fitness before surgery to affect early postoperative mobilization, provide a baseline of optimized preoperative exercise capacity for comparison with postoperative exercise capacity, and to maintain comparability between medical and surgical patients.

All participants engaged in the pulmonary rehabilitation program, which was conducted in three phases: pre-randomization (16 to 20 sessions over 6 to 10 weeks); post-randomization (10 sessions over 8 to 9 weeks); and long-term maintenance (duration of the trial). The rehabilitation programs were supervised by a NETT clinical center; portions of the program were carried out at a NETT-certified rehabilitation facility closer to the participant’s home. The long-term maintenance program was to be conducted at home or at fitness centers with continued monitoring and support performed by a NETT clinical center. Specific components of the pulmonary rehabilitation program included the following:

- Comprehensive evaluation of medical, psychosocial and nutritional needs
- Setting of goals for education and exercise training
- Exercise training (lower extremity, flexibility, strengthening, and upper extremity)

- Education about emphysema, medical treatments and NETT
- Psychosocial counseling
- Nutritional counseling

Pre-randomization baseline measurements were completed after pulmonary rehabilitation, and patients were re-examined at six months, 12 months, and yearly thereafter. Patients who met the inclusion criteria after rehabilitation were randomized 1:1 to medical therapy and medical therapy plus LVRS. Patients were scheduled for surgery within two weeks of randomization. Only stapled LVRS with excision was used in the trial. In addition, the protocol established that all patients treated surgically would undergo bilateral reduction surgery due to evidence available that the bilateral procedure afforded greater and more consistent benefits that the unilateral procedure.

Surgical approaches were median sternotomy (MS) or video-assisted thoracoscopic surgery (VATS). In centers that performed both methods of surgery, investigators randomized patients 1:1 to MS and VATS. Both surgical and medical groups underwent post-randomization rehabilitation for eight to nine weeks including exercise training once weekly. Patients were encouraged to continue long-term rehabilitation at home.

Statistical considerations

Although the primary statistical objective of the study was to ascertain differences between the two groups in survival and maximum exercise capacity, the structure and size of the trial permitted the conduct of subset analyses, as well as comparisons of morbidity, mortality and outcomes within the surgery group between MS and VATS. These differences would be assessed with lower power than the primary comparison, but would permit significant differences to be detected as well given the large sample size of the overall study.

An important objective of the trial was thus to gather information to characterize any subset of patients who might receive disproportionate benefit (or risk) from the surgical procedure. In selecting patients for surgery, investigators used clinical tests generally available to community practitioners. The inclusion criteria for the trial were broad enough to allow the evaluation of subgroups of patients who have traditionally been considered candidates for surgery but who were present in only small numbers in previous studies. The investigators prospectively announced their intent to conduct separate analyses in a pre-defined subset of patients who were thought most likely to benefit. The association between benefit and baseline prognostic factors was assessed using a multiple logistic regression model. The protocol established that a similar procedure would be used to identify subsets of patients who might be at high short-term risk from treatment.

For purpose of analysis, patients were counted in the treatment group to which they were randomly assigned without regard to dropouts, drop-ins, or course of therapy (i.e., intention-to-treat principle). All events occurring from the time of randomization were counted in the treatment group to which the patient was assigned. Outcomes were monitored by an independent data and safety monitoring board (DSMB).

a) Patients at High Risk of Death after Lung Volume Reduction Surgery.

The independent DSMB was charged with periodically reviewing subgroups of patients who might benefit from or be harmed by LVRS. As a result of such review, a set of clinical characteristics was identified defining a group of patients with a high mortality rate and little benefit after LVRS. Consequently, before the trial was completed, the NETT investigators published an interim article describing this subgroup of high-risk patients and changed the inclusion and exclusion criteria for entry into the trial so that this patient population was no longer recruited into the trial.[23]

The investigators had provided the DSMB at the outset of the study with guidelines to be used in identifying subgroups whose risk might be increased by the procedure. Both the investigators and the DSMB considered a 30-day surgical mortality greater than 8 % to be unacceptable; a guideline was therefore instituted to terminate randomization if the lower 95 % confidence limit for 30-day mortality exceeded 8 %.

The DSMB also examined a number of additional variables to identify subgroups of patients who might benefit or be at risk from LVRS. The candidate variables the DSMB reviewed and thought could potentially produce benefit were age 70 or less, postbronchodilator FEV1 of 15 to 35 % of the predicted value, a partial pressure of arterial carbon dioxide of 50 mm Hg or less, a residual volume greater than 200 % of predicted, a low radionuclide perfusion ratio (0.2 or less), a heterogeneous pattern of emphysema on CT scanning, and evidence of hyperinflation on chest radiography. Other variables were carbon monoxide diffusing capacity, maximal work capacity, quality of life, race or ethnic group, and sex. The DSMB reviewed subgroups of patients derived from these candidate variables every three months for evidence of increased risk or benefit from LVRS with the understanding that enrollment would be terminated early if such benefit or risk were found.

Based on sensitivity analyses modifying the cut-off points of a small number of variables that were associated with increased 30-day mortality, the DSMB found in May 2001 that the combination of three of these risk factors could define a subgroup of patients who exceeded the stopping guideline for that outcome. This high-risk subgroup was defined by a combination of low FEV1 and either homogeneous emphysema or low carbon monoxide diffusing capacity.

Results

Between January 1998 and June 2001, 1033 patients had undergone randomization at 17 clinical centers. 140 patients (13.6%) were in the group at high risk for death after LVRS (70 in the surgical group, 70 in the medical group). The group of high-risk patients constituted the population of interest whose trial results were reported in October 2001.

All 140 patients had an FEV1 that was no more than 20% of predicted value. Ninety-four also had evidence of homogeneous emphysema on CT scanning, and 87 had carbon monoxide diffusing capacity < 20%. Forty-one patients met all three risk factors. Thus, the high-risk group was composed of patients who had an FEV1 that was equal or less than 20% of predicted in combination with either homogeneous emphysema or a carbon monoxide diffusion capacity equal to or less than 20% of predicted value. The baseline characteristics of these patients were similar in the two treatment groups.

Perioperative mortality. There were no deaths in the medical therapy group during the first 30 days after randomization. In contrast, the 30-day mortality rate after surgery was 16 % (95% confidence interval, 8.2 to 26.7%; p<0.001). Patients with all three high-risk characteristics had a 30-day mortality rate of 25% (95% CI, 8.7 to 49.1%). Thus, five of the 20 patients in the surgery group who had all three factors died within 30 days after surgery. The 30-day mortality rate after surgery was similar among patients who had undergone VATS and those who had MS (p>0.99).

Overall mortality rate was 0.43 deaths per person-year among patients assigned to undergo surgery compared with 0.11 deaths per person-year among those assigned to medical therapy. The relative risk of death between groups was 3.9 (95% CI, 1.9 to 9.0). For roughly 90% of patients in both groups, the cause of death was classified as respiratory.

Exercise capacity. Sixty patients assigned to surgery and 51 patients assigned to medical therapy were included in the six-month analysis of outcomes. When the analysis was confined to survivors who completed the evaluation, there was a small improvement in exercise capacity from baseline to six-months in the surgical group. This group reported an average increase of 4.5 plus or minus 13 watts compared with a decrease of 4.4 plus or minus 14.8 watts in the medical therapy group (p=0.06).

Quality of life. No significant difference between groups existed in the score for the Quality of Well-being questionnaire (scores can range from 0 to 1; decrease of 0.01 units observed in both groups; p=0.94)

Respiratory function. In the analysis of survivors only, 35% of 34 patients able to perform the test in the surgery group had an increase in FEV1 of at least 200 ml at six months, compared with none of 26 patients in the medical group (p=0.01). [24]

In sum, the authors noted that within 30 days after surgery, 16% of the patients in the surgical group had died. After six months, only 33% had an improvement in exercise capacity, 23% had either no change or a decrease in exercise capacity, 8% were unable to complete the testing, and 35% had died. The health related quality of life improved in only 28% of these patients, with 72% either dying or having no change or a decrease in the quality of lifer. The medical-therapy group had a higher percentage of poor functional outcomes but fewer deaths. The distribution of the changes from baseline in the scores for exercise capacity and FEV1 favored neither treatment group when the authors accounted for deaths and missing information. Because of the generally unfavorable outcomes, the NETT ceased to enroll these high-risk patients in the clinical trial as of July 2001.

b) Effects of LVRS Versus Medical Therapy.

The study proceeded to meet its main objectives of establishing the impact of LVRS on mortality and the magnitude and durability of benefits for all NETT participants. 1218 patients with severe emphysema underwent pulmonary rehabilitation and were randomized to receive LVRS or continued medical treatment at 17 centers during a 4.5-year period of implementation (from January 1998 through July 2002). In May 2003, investigators published the results of the completed clinical trial for all randomized patients.[25]

Methods

As mentioned above, the primary outcomes for the trial were mortality and maximum exercise capacity two years after randomization. Secondary outcomes included six-minute walk distance, pulmonary function, quality of life and dyspnea. Eight centers performed LVRS by MS alone, three centers by VATS alone, and six by MS or VATS selected randomly. Adherence to medications, tobacco abstinence and pulmonary rehabilitation treatment were monitored through regular telephone calls and clinic visits.

Total 30-day and 90-day mortality rates from all causes were measured beginning at randomization for both treatment groups. The risk ratio of death between treatment groups was estimated from all-cause mortality rates in each group after a mean of 29.2 months of follow-up.

All primary outcomes in addition to mortality were dichotomized, such as improved versus not improved, and were defined for all patients, not just survivors. Thus, those who were reported as not improving included patients unable to complete the evaluation or who have died. The clinical judgment of the investigators determined the cut-point for classifications derived from measured outcomes defining improvement. For instance, improvement in maximum exercise capacity was defined as an increase in maximum work of more than 10 watts above the post-rehabilitation baseline level. Improvement in health-related quality of life was defined as a decrease in SGRQ score of more than eight units below post-rehabilitation baseline.

The investigators and the DSMB judged that changes meeting or exceeding these thresholds constituted clinically important improvements for patients with this severe impairment. The thresholds were greater than those typically used as minimal clinically important differences but were selected to represent improvement appropriate to justify the high risks of surgery for patients with severe emphysema. Patients who died or were missing data required for the assessment were counted as not improved with regard to these functional outcomes. All analyses were conducted comparing the treatment groups to which patients were originally assigned by randomization (intention-to-treat principle).

Subgroups of patients with differential risk or benefit were identified by the results of logistic regression analyses relating certain patient baseline characteristics to outcomes such as mortality, exercise capacity or improvement in health-related quality of life (SGRQ) measured at six, 12 and 24 months. A number of these characteristics or prognostic factors were identified by prior hypothesis and specified in the trial protocol (e.g., age, FEV1 percent predicted, emphysema distribution on CT scan). Measures of distribution of emphysema included radiologist assessment of upper lobe predominance, homogeneous vs. non-homogeneous distribution and radionuclide perfusion ratio.[26] The DSMB and the investigators added other baseline prognostic factors after trial initiation but well before completion of data collection (e.g., carbon monoxide diffusing capacity percent predicted, maximum exercise capacity at baseline).

Results

3777 patients were evaluated for the study and 1218 were randomized to receive LVRS (N=608) or continued medical treatment (N=610). Excluding the high-risk subgroup, investigators found additional subgroups in the remaining non-high risk patients in which the relative benefits of LVRS differed qualitatively. These differences were based on a combination of (1) distribution of emphysema (upper-lobe predominant or not) and (2) post-rehabilitation baseline exercise capacity (low or high). The cut point between low and high baseline maximum exercise capacity separating patients with differential mortality risk was found to be the gender-specific 40th percentile measure among study participants25 watts for women and 40 watts for men. Below are study findings for all patients as well as final results for high-risk and the additional four non-high subgroups.

1. All patients (N=1218)

Mortality. The 90-day mortality rate in the LVRS group was 7.9% (95% CI: 5.9 to 10.3%) and was significantly higher than the 90-day rate for medical patients (1.3%; p<0.001). The overall mortality was 0.11 deaths/person/year in both treatment groups based on a mean follow-up of 29.2 months (risk ratio=1.01, p=0.90). There was no statistically significant difference in overall mortality despite increased early mortality in the LVRS group (table 1).

Exercise capacity improved more that 10 watts in 28%, 22% and 15% of surgery patients after 6, 12 and 24 months respectively, compared with 4%, 5% and 3% of medical patients (p<0.001 for all comparisons) (table 2).

Quality of life, symptoms, respiratory function. LVRS patients also showed statistically significant improvements compared to medical patients in general and health-related quality of life, dyspnea and FEV1.

2. High-risk patients. (N=140)

The subgroup of 140 patients with FEV1 = or < 20% of predicted value and either diffuse emphysema or $D_LCO \leq 20\%$ predicted was previously reported to have high mortality with little chance of functional benefit. The updated mortality and functional improvement analyses for this subgroup supported the previous findings.

3. All non-high risk patients. (N=1078)

Mortality and morbidity. The 90-day mortality rate in the LVRS group was 5.2 % and 1.5% in the medical group (p=0.001). Two months after randomization, 14.3 % of the surgical group versus 3.3% of the medical group were hospitalized, living in a nursing home or rehabilitation facility or unavailable for interview but not known to be dead (p<0.001); at 8 months, the percentages were 3.3 and 3.7% respectively. Total mortality among non-high risk patients during the trial was 0.09 deaths/person/year for LVRS patients versus 0.10 deaths/person/year for medical patients (RR=0.89; p=0.31).

Exercise capacity, quality of life, dyspnea and FEV. Changes at 6, 12 and 24 months favored the surgical group in all these outcomes (table 2). For instance, exercise capacity after 24 months improved more than 10 watts in 16% of surgical patients versus 3% of medical patients (p<0.001). Limiting analysis to survivors able to complete the follow-up assessments, the pattern of changes in outcome measures showed a progressive decline from baseline in the medical group while the LVRS group showed improvements over baseline but also gradually declined over 24 months.

4. Pre-operative predictors of outcomes in non high-risk patients

The only individual baseline factors associated with differential relative mortality comparing treatment groups were distribution of emphysema on CT scan (upper-lobe predominant or not) and post-rehabilitation baseline exercise capacity (low or high). The only individual baseline factor associated with differential improvement in maximum work at 24 months was distribution of emphysema. Considering these two baseline patient characteristics in combination defines four subgroups with strong evidence of differential effects on relative mortality and exercise capacity at 24 months (see table 1 for effects on mortality; table 2 for exercise capacity; table 3 for quality of life outcomes).

a. Patients with upper-lobe disease and low exercise capacity (N=290).

Mortality. LVRS patients had lower risk of death (risk ratio=0.47, p=0.005) (table1).

Exercise capacity. The surgical group was more likely to have had more than a 10-watt improvement in maximum work at 24 months (30% vs. 0%, p<0.001) (table 2).

Quality of life. Surgical patients were more likely to have an 8-point improvement in SGRQ score at 24 months (48% vs. 10%, p<0.001) compared to patients with upper-lobe disease and low exercise capacity in the medical management group (table 3).

b. Patients with upper-lobe disease and high exercise capacity (N=419).

Mortality. These patients had similar mortality regardless of treatment (risk ratio=0.98, p=0.70).

Exercise capacity. LVRS patients were more likely than medical patients to have more than 10 watts improvement in maximum work at 24 months (15% vs. 3%, p=0.001).

Quality of life. LVRS patients were more likely to have an 8-point improvement in SGRQ score for quality of life at 24 months (41% vs. 11%, p<0.001).

c. Patients with non-upper-lobe disease and low exercise capacity (N=149).

Mortality. Surgical and medical patients had a similar risk of death (risk ratio=0.81, p=0.49)

Exercise capacity. Both groups had a similar chance of more than 10 watts improvement in maximum work at 24 months (12 % vs. 7%, p=0.50).

Quality of life. LVRS patients were more likely than medical patients to have an 8-point improvement in SGRQ score at 24 months (37% vs. 7 %, p=0.001).

d. Patients with non-upper-lobe disease and high exercise capacity (N=220).

Mortality. LVRS patients had a higher risk of death compared to medical patients (risk ratio=2.06, p=0.02).

Exercise capacity. Both groups showed a low chance of having more than a 10-watts improvement in maximum work at 24 months (3% in both groups; p=1.00).

Quality of life. Surgical patients had similar chance of an 8-point improvement in SGRQ score compared to those medically managed (15% vs. 12%, p=0.61).

In summary, LVRS did not confer an overall survival advantage over medical therapy but increased the chance of improvements in exercise capacity, lung function, quality of life and dyspnea. A survival advantage was clear only for patients with both upper-lobe predominant emphysema and low baseline capacity. Patients with upper-lobe emphysema, in particular those with low baseline exercise capacity, had the greatest chance of functional benefit. Patients with non-upper-lobe emphysema and higher baseline exercise capacity as well as the previously reported high-risk subgroup were seen as poor candidates for LVRS due to increased mortality and negligible functional gain.

4. Position Statements

In April 1998 the World Health Organization and NHLBI supported a workshop (the Global Initiative for Chronic Obstructive Lung Disease) to discuss the diagnosis, management and prevention of COPD.[27] The executive summary from the workshop describes LVRS as an unproven palliative procedure that cannot be recommended for widespread use until the results of large randomized studies are known.

5. Expert Opinion

The American Thoracic Society (ATS) submitted written support of Medicare coverage of LVRS based on the results and patient selection criteria of the NETT. The ATS also supported using appropriate criteria to qualify facilities that provide LVRS, including demonstrated experience with LVRS, acceptable mortality/morbidity outcomes, demonstrated access to appropriate range of services and specialists, and anticipated volume of LVRS candidates. The ATS also recommended that pulmonary rehabilitation services be a covered Medicare service for all patients with severe obstructive lung disease.

The American Association for Thoracic Surgery (AATS) submitted comments in support of Medicare coverage of LVRS based upon the improved quality of life and physical functioning shown in the NETT in addition to coverage of pulmonary rehabilitation services for patients considered for LVRS. The AATS urged monitoring and review of the designated LVRS centers for patient outcomes.

The Society for Thoracic Surgeons (STS) commented that LVRS should be covered for a broader group of patients than the NETT study to include patients considered to be good candidates based on reasonable scientific information and individual physician and surgeon assessment. The STS recommended that centers that perform surgery should include NETT centers, Medicare approved lung transplant centers, and other centers to be approved, provided they are staffed by board certified thoracic surgeons with access to pulmonary rehabilitation, a multidisciplinary team of pulmonary physicians and thoracic surgeons, and finally a history of performing at least 100 non-LVRS pulmonary resections annually. STS also recommended the use of the STS National Database to collect data on patient outcomes to ensure appropriate application of LVRS.

CMS received comments from the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) in support of coverage of LVRS based upon data from the NETT demonstrating the benefits of LVRS including improved quality of life and physical functioning. AACVPR favors Medicare coverage of pulmonary rehabilitation services for all potential LVRS patients in addition to patients with chronic obstructive pulmonary disease.

The National Association for Medical Direction of Respiratory Care (NAMDRC) submitted comments in support of Medicare coverage of LVRS based on the NETT and urged CMS to expand coverage to facilities beyond those that participated in the NETT. NAMDRC also supported coverage of initial pulmonary rehabilitation services prior to LVRS.

CMS received comments from the American College of Chest Physicians (ACCP) supporting Medicare coverage of LVRS based on the NETT. ACCP also recommended that CMS expand coverage to include facilities that did not participate in the NETT. In addition, the organization supported coverage of pre and post-operative pulmonary rehabilitation services for LVRS patients and for patients with chronic lung disease who meet NETT criteria.

6. Public Comments

CMS received 65 letters from patients and caregivers of patients suffering from COPD or emphysema. Some of these letters included testimonials from patients that have had LVRS and others were from patients who would like the opportunity to receive surgery as a Medicare covered benefit. Many patients specifically recommended that quality of life be considered along with survival when reviewing data from the NETT.

CMS also received letters supporting Medicare coverage of LVRS from nine physicians and one nurse. Some physicians cautioned that appropriate patient selection and facility criteria were critical in achieving good health outcomes and that Medicare should carefully implement such criteria.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations made by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.” § 1862(a)(1)(A).

This section summarizes the agency's evaluation of the evidence available on the effect of LVRS on final health outcomes for Medicare beneficiaries. We address the three specific questions that guided the overall assessment and the related evidence that led to the coverage conclusions. We first discuss the reasons for utilizing primarily the NETT findings in support of our coverage decision and for limiting the population covered to patients who satisfy the inclusion and exclusion criteria for the trial. We also address the provision of certain pre-operative and post-operative specialized services NETT patients received during the trial that future patients undergoing LVRS would need to receive to match trial results. Secondly, we discuss and conclude that the evidence provided by the NETT is adequate to distinguish subgroups within the population eligible for the trial for whom final health outcomes differ markedly. Accordingly, we justify coverage for those patients that are likely to benefit from the procedure and exclude from coverage those subgroups of patients who are at risk for harm or who are not likely to benefit from surgery. Finally, we explain why facilities ought to meet certain standards as a condition of coverage.

Does LVRS with medical therapy improve health outcomes in Medicare patients with severe emphysema compared to medical therapy alone?

The NETT is the largest randomized controlled trial to date comparing medical therapy plus LVRS vs. medical therapy alone. In addition to its size and methodologically sound assignment of patients to experimental and control groups, the study presents a number of strengths when compared to studies previously conducted on the effect of LVRS on health outcomes. Investigators thoroughly specified inclusion and exclusion criteria and the process of selection of study subjects, ensured comparability of both groups while eliminating usual confounding variables (e.g., similar requirements for ancillary respiratory services), described interventions and outcomes in detail, and utilized appropriate outcome measures. They also provided adequate follow-up to document the durability of results over a two-year period, ensured that little loss of patients to follow up occurred, and performed appropriate statistical analyses (such as utilizing intention-to-treat principles.) Importantly, the trial sought to answer questions not only of overall effectiveness, but also of appropriate patient selection.

The NETT thus addressed a variety of gaps in the evidence available in the literature before its implementation. Prior studies had been lacking in direct information on quality of life measures, relying instead on pulmonary function tests, measures that do not necessarily reflect functional ability in activities of daily living, which in turn affect quality of life. Results from the six-minute walk test frequently reported in the literature as the primary measure of exercise capacity were also in question given the variations produced by test strategy and clinician encouragement. Instead, the NETT design utilized direct measures of quality of life and selected maximum, incremental, symptom-limited exercise testing by bicycle ergometer as the most reliable measure of exercise tolerance.

In addition, the LVRS literature had reported improvements in exercise capacity as measured by the six-minute walk test, dyspnea scores and respiratory function only as short-term outcomes. Most studies failed to follow a large percentage of treated patients beyond three months after surgery creating the possibility of considerable bias for reported outcomes. Accordingly, the NETT trial protocol sought to follow patients for a two-year period to assess whether any improvements persisted, were augmented or diminished over time.

Finally, the literature available prior to initiation of the NETT had shown that a substantial proportion of patients undergoing LVRS experienced no functional improvement postoperatively. Accordingly, an important purpose of this trial was to develop variables that could identify patients who would be more likely to demonstrate improved survival with surgery as well as clinically significant improvement. Therefore, the high quality of design, implementation, analysis and reporting of the NETT makes the evidence provided by the trial adequate to permit conclusions concerning the effect of LVRS on health outcomes for those patients who met the criteria for inclusion in the trial. Thus, CMS concludes that LVRS is reasonable and necessary for the patients that showed positive net health outcomes in the trial (further defined in the following section).

The large proportion of Medicare beneficiaries included in the NETT is another valuable and rare characteristic of the study that permits generalization of the experience of study participants to the Medicare population without the need of extrapolation based on biological plausibility arguments. Thus, the evidence from the NETT is directly applicable to those Medicare patients who satisfy the inclusion and exclusion criteria of the trial. These criteria are listed in Tables 3a and 3b, slightly modified to allow for additional patient and physician discretion.

Given the validity of the NETT study results and the applicability of those results to the Medicare population, our critical appraisal of the literature relied in great measure on NETT findings and its identification of subgroups more likely to derive benefits or harms from LVRS. Because the design of the NETT included specific criteria to define the population studied, its findings were limited to that population. We did not consider either the NETT or other available evidence adequate to draw conclusions on the effectiveness of LVRS on patients with pulmonary disease beyond the trial population. Thus, the evidence supporting a finding that LVRS is reasonable and necessary is limited to patients who satisfy the inclusion and exclusion criteria under the NETT protocol.

Since NETT participants completed a specialized pre-operative and post-operative treatment program, the evidence supporting a finding that LVRS is reasonable and necessary is limited to patients who receive similar services. However, an evaluation of the range of services encompassed by the concept referred in the trial protocol as pulmonary rehabilitation was not among the objectives of the NETT and was not part of the evidence review on LVRS undertaken by CMS staff. Rather, all patients in the NETT were required to complete a specified program of diagnostic and therapeutic services to ensure that both groups were treated equally in this regard (to avoid confounding) and to maximize the surgical patients' potential to successfully undergo and recover from surgery. The results of the trial are most readily applied to patients receiving similar pre and post-operative services.

Therefore, CMS will consider LVRS reasonable and necessary for the populations who would satisfy the inclusion and exclusion criteria under the NETT protocol only if coupled with pre-operative and post-operative services that are similar to those provided under the NETT and required by the trial protocol. The program must include a 6 to 10 week series of at least 16, and no more than 20, preoperative sessions each lasting a minimum of two hours. It must also include at least 6 and no more than 10 postoperative sessions each lasting a minimum of two hours, within 8 to 9 weeks of the LVRS. This program must be consistent with the care plan developed by the treating physician following performance of a comprehensive evaluation of the patient's medical, psychosocial, and nutritional needs. The program of perioperative diagnostic and therapeutic services must be furnished under the medical direction and supervision of the facility where the surgery takes place to ensure that the facility has complete diagnostic and medical information to maximize the surgical patients' potential to successfully undergo and recover from surgery.

What subgroups of patients with severe emphysema are likely to benefit from the procedure?

In our review of the NETT data, we considered the statistical validity of identifying subgroups within the trial population and relating health outcomes to a number of patient variables that were present at baseline. During the course of the trial, the investigators first identified a group of patients with certain baseline characteristics linked to high risk for surgery, which resulted in adjustments to the inclusion and exclusion criteria and subsequently categorized the remaining non-high risk patients into four subgroups. Subgroup analysis requires validation since it increases in principle the likelihood that associations between risk factors and health outcomes will achieve statistical significance on the basis of chance alone.

Concern about potentially generating such results may arise when more than one association (in this case involving several risk factors with various potential cutoff points) is tested in a study. The concern about generating these errors is particularly justified when hypotheses are formulated after the data are analyzed (post-hoc hypotheses).[28] However, when research hypotheses are formulated during the design phase of the study, are based on clinical experience and are reasonably related to evidence from other sources, the concern lessens that the discovery of risk subgroups might represent this type of error.

Our confidence in the validity of the NETT subgroup data was relatively high because trial objectives included identification by prior hypothesis of subgroups with differential harm or benefit from LVRS. The NETT investigators defined the candidate risk factors prior to the trial and also limited the number of possible statistical tests. In addition, the low p-values and large risk ratios found in some of the associations revealed by the study, together with their biological plausibility, lend support to the findings from subgroup analyses. For instance, in patients with homogeneous disease, shown in the study to be associated with worse health outcomes, LVRS is likely to involve resection of functional lung tissue to a larger extent than in patients with heterogeneous emphysema. Similarly, it is biologically plausible that in patients with low carbon monoxide diffusing capacity, resection of lung tissue may restrict the pulmonary surface area available for gas exchange enough to worsen hypoxemia and compromise survival. Finally, longitudinal views of the data also suggest consistency and increasing statistical significance of the relevant associations over time (e.g., increased mortality rates in high-risk patients persist beyond the 30-day postoperative period).[29]

These considerations provide assurance that the type of subgroup analysis performed for the NETT is likely to be valid. Therefore, we believe that the evidence provided by the NETT is adequate to distinguish among subgroups of patients with severe emphysema. The evidence is also adequate to conclude which of these subgroups are likely to benefit or be at high risk of harm from the surgical procedure and to support coverage or non-coverage for these subgroups accordingly. Below we indicate why patients with upper-lobe predominant emphysema are likely to benefit from LVRS and why other subgroups within the NETT (including high-risk patients and those with non-upper-lobe distribution of emphysema and high-exercise capacity) are likely to be harmed by the procedure. We also explain why the evidence provided by the NETT is adequate to conclude that the benefits of LVRS outweigh its risks for the remaining subgroup of patients, i.e., those with low exercise capacity and non-upper lobe distribution of emphysema.

In the reported trial results, the only individual baseline factor associated with differential improvement in mortality and/or maximum work at 24 months was distribution of emphysema. CMS thus considers that the evidence provided by the NETT is adequate to conclude that LVRS is likely to improve net health outcomes (i.e., survival, exercise capacity or quality of life) in non-high risk patients who meet inclusion criteria outlined in the study and who present with severe bilateral upper-lobe predominant emphysema. Upper-lobe predominance may indicate clearer target areas for surgical resection, more accessible areas for excision, or healthier remaining lung.

The agency considers the evidence adequate to conclude that LVRS is likely to be more harmful than beneficial in high-risk patients as defined by the NETT. This subgroup had high mortality compared to the medical patients in the same category and a small likelihood of functional improvement in exercise capacity or quality of life. Similarly, the evidence is adequate to conclude that LVRS is likely to worsen health outcomes for non-high risk patients who meet the NETT inclusion criteria and present at baseline with non-upper lobe predominant severe emphysema and high exercise capacity (as defined in the final study report). These surgical patients had twice the risk of death and the same chance of improvement in exercise capacity or quality of life compared to medical patients in the same subgroup.

The evidence available on the remaining subgroup of patients with non-upper-lobe emphysema and low exercise capacity is less conclusive on the net health outcomes resulting from LVRS from a population-based perspective. The surgical patients in this subgroup experienced no survival or exercise capacity benefit. However, a larger proportion of these patients (37%) than that in the medical group (7%) showed a considerable improvement in quality of life measures.

Although the difference between medical and surgical groups in this self-reported outcome measure is considerable, its magnitude may have been amplified by the design of the study. Specifically, the design of the NETT did not preclude patients or investigators from knowing which participants were in the experimental group and which in the control group. The non-masked nature of the trial left the experience of the surgical procedure as a potential source of differential bias between the medical and surgical groups, particularly with respect to outcomes based on participants' self report. It is possible that the experience of a major surgical procedure which patients hoped beneficial could account for the differences in perception of post-treatment quality of life between medical and surgical patients.[30] The NETT trial design thus does not allow us to determine to what extent features specific to LVRS resulted in improvement of net health outcomes for patients in this subgroup.

This potential observer bias notwithstanding, patients with non-upper lobe predominant emphysema and low exercise capacity were much more likely than their medical counterparts to experience considerable quality of life improvement while subject to no significant added risk of mortality or functional decline. The evidence reviewed is thus adequate to conclude that LVRS is reasonable and necessary for this subgroup. However, whether surgery is reasonable for this patient population will probably depend to a larger degree than for patients with upper-lobe predominant emphysema on the weight attributed to the risks and potential benefits of the intervention in the beneficiary's fully informed individual judgment.

Should the performance of LVRS be limited to specific facilities?

Even with the experience of the NETT investigators and the oversight of the protocol, the benefits of LVRS came at the price of short-term mortality and morbidity. Thus, the results of LVRS for the subgroups that benefited under trial conditions could be negated if broad utilization in non-specialized centers increased morbidity and mortality. The experience with LVRS in the mid 1990s further justifies the concern about premature dissemination of this procedure from selected centers to all hospitals. As mentioned earlier, a Medicare claims analysis for the procedure performed at the time found that mortality rates at three and 12 months post-LVRS were 14.4% and 23% respectively (roughly double the mortality rate reported by NETT). For these patients, acute-care hospitalizations as well as long-term care and rehabilitation services were greater post-surgery than pre-surgery.

Furthermore, the peer-reviewed literature has demonstrated that caution is advised in translating the efficacy of carefully controlled studies to effectiveness in everyday practice. Medicare patients' perioperative mortality for other surgical procedures was shown to be substantially higher than that reported in well-controlled clinical trials.[31] Processes that operate at both the institution (e.g., higher volume of procedures performed) and patient level (e.g., absence of comorbidities, detailed explanation of intervention on the part of investigators) may explain the lower mortality rates observed in the trials. CMS thus considers that facility criteria should be established for LVRS to limit the risk that Medicare patients' perioperative mortality and morbidity following LVRS become substantially higher than that reported in the randomized trials discussed in this memorandum. However, since these criteria do not currently exist in the Medicare program, we will solicit comments on the appropriate method of establishing them, and on the method of accrediting facilities once those criteria have been established.

Until this information gathering process is underway, we recognize that sites participating in NETT have met both facility and staff criteria as part of a rigorous selection process established by NHLBI prior to the start of the trial. Since the results of the NETT depended upon performance of the selected programs, CMS considers that LVRS is reasonable and necessary when performed in these sites.

Lack of an accreditation process limits the ability to generalize the results of the NETT for LVRS procedures performed outside the trial sites. However, CMS has already developed criteria for approval of lung transplantation centers. We expect that the kind of integrated team assembled at the trial sites with expertise in pulmonary medicine – especially as it related to end-stage emphysema, pulmonary mechanics, diaphragm mechanics, pulmonary rehabilitation, thoracic surgery, critical care anesthesia, quality of life and dyspnea assessments, and pulmonary radiological assessment – could be readily established or would be present at current lung transplant facilities. In addition, we understand that experienced lung transplant surgeons could perform LVRS with beneficial results given the overlap of skills required for both surgical procedures. Thus, in order to provide adequate access to LVRS while preserving a high standard of care, CMS considers that the NETT results should be applicable to lung transplant centers.

In light of the considerable risks of the LVAD procedure, an important facility requirement is a patient selection protocol, including an extensive informed consent process, to identify patients for whom the procedure is reasonable and necessary. Patient education prior to the procedure is crucial. Informed consent must be truly informed and be guided by competent individuals with the knowledge and time to provide extensive, detailed information to the beneficiary. We believe that the favorable outcomes shown through the clinical trial we reviewed can only be obtained through careful patient selection protocols that included detailed informed consent processes.

Each institution's informed consent process should include a written document that would be understandable to all potential LVRS patients. Such a document should be understandable for people at all educational levels and appropriate for the potential recipient's level of education. Apart from the need to employ specifically defined medical terms, the document should in most circumstances be written for readers with no higher than an 8th or 9th grade level of education. If the potential recipient does not speak English, there should be an independent interpreter to facilitate understanding in the patient's language. Where appropriate, translations of such a document and accompanying materials should be made available.

CMS further expects that, based on our review of patient selection and informed consent protocols in the clinical trials reviewed, the following elements be incorporated in the informed consent document given to the potential LVRS recipient, with specific descriptions that would ensure the patient's awareness of:

(1) The evaluation process
(2) The surgical procedure
(3) Alternative treatments
(4) Potential medical risks such as infection and bleeding with provision of national and center-specific rates
(5) National and center-specific short-term and long-term mortality
(6) National and center-specific outcomes other than mortality
(7) National and center-specific hospital lengths of stay
(8) Potential risk factors that could affect the immediate or future success of the surgery or the health of the patient, such as the patient's history
(9) His or her right to refuse the surgery

CMS recognizes that institutions operating in different states across the nation may have different laws and needs that will affect the precise wording of the informed consent document(s) they will use. For that reason, these consent documents must be tailored to the specific needs and regulations under which each facility operates.

Moreover, CMS does not believe that forms are a substitute for in-person communication between physicians and other involved professionals and the potential recipient and his family. These forms should be viewed instead only as the written evidence of discussions and any other communicational exchange (including, for example, provision of videotapes describing the procedure) leading to informed consent based upon full disclosure. Due to the significant time commitment required for full disclosure, CMS expects that each facility will train and assign to each potential LVRS patient an independent advocate who will assist the operating team and facility supporting staff in ensuring that full disclosure occurs. These informed consent requirements will be made a part of the facility accreditation criteria.

In summary, to the extent that CMS has determined that LVRS is reasonable and necessary (as discussed in the preceding sections), that conclusion is limited to LVRS when performed at facilities that were identified by NHLBI to have met the standards for participation in the NETT and at sites that have been approved by Medicare as lung transplant facilities until such time as CMS implements accreditation standards. After CMS implements accreditation standards, LVRS will be reasonable and necessary only at accredited facilities.

Evidence Tables [PDF, 231KB]

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[1] NETT Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *New England Journal of Medicine.* May 2003. Investigators restricted the inclusion and exclusion criteria present in the original NETT protocol in light of interim findings of a high-risk group of participants in the study. CMS further modified the NETT criteria to a limited extent in order to streamline policy implementation and allow for additional physician and patient discretion. Table 3 lists the criteria pertinent to this decision memorandum.

[2] P Adams , *et al*. Current estimates from the 1996 National Health Interview Survey. *Vital Health Stat* 10 (200) 1999. National Center for Health Statistics.

[3] D Hoyert *et al*. Deaths: Final Data for 1999. *National vital statistics reports*. 2001. National Center for Health Statistics.

[4] See e.g., Cooper et al. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surgery.* 1995.

[5] Coverage Issues Manual §35-93

[6] Holohan and H Handelsman. *Lung-Volume Reduction Surgery for End-stage Chronic Obstructive Pulmonary Disease.* AHCPR. September 1996 AHCPR.

[7] *Hulley et al. Designing Clinical Research.* Lippincott Williams & Wilkins. Second edition. 2001.

[8] D. Wood. Lung volume reduction surgery: Tempest in a teapot. *Journal of Thoracic and Cardiovascular Surgery.* March 2003.

[9] Given that attrition may increase the risk of overestimating the efficacy of a treatment, some peer-reviewed journals will not publish trials with more than 20% of patients lost to follow-up. Sackett et al. *Evidence-based Medicine, How to Practice and Teach EBM.* 2000.

[10] Lacasse et al. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. *Lancet.* 1996.

[11] Hulley et al. *Designing Clinical Research.* 2001.

[12] Systematic reviews often constitute the core of technology assessment reports. Two of the reviews summarized in this memorandum were part of formal technology assessment reports produced by the Blue Cross and Blue Shield Association (BCBS) Technology Evaluation Center and ECRI, organizations that specialize in health technology assessment.

[13] Technology Evaluation Center, BCBS Association. Lung Volume Reduction Surgery for Severe Emphysema. **Technology assessment report to the BCBS Medical Advisory Panel. March 1999.**

[14] J Young et al. Lung volume reduction surgery for chronic obstructive pulmonary disease with underlying severe emphysema. Thorax. **September 1999.**

[15] ECRI Health Technology Assessment Information Service. Lung Volume Reduction Surgery for Emphysema. **Technology Assessment Report. September 2001.**

[16] D Geddes et al. Effect of lung volume reduction surgery in patients with severe emphysema. *New England Journal of Medicine.* July 2000; Pompeo et al. Reduction pneumoplasty versus respiratory rehabilitation in severe emphysema: a randomized study. *Annals of Thoracic Surgery.* September 2000; Criner et al. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine.* December 1999.

[17] Wilkens et al. Lung volume reduction surgery versus conservative treatment in severe emphysema. *European Respiratory Journal.* December 2000

[18] B Meyers et al. Outcome of Medicare patients with emphysema selected for, but denied, a lung volume reduction operation. *Annals of Thoracic Surgery.* 1998.

[19] Search performed on 3-17-03

***[20] NETT Research Group: "Rationale and Design of the National Emphysema Treatment Trial." Chest.* December 1999.**

[21] *Ibid.*

[22] The 6-min walk distance test was included because of its widespread use by investigators previously reporting on the results of LVRS but was designated as a secondary measure of outcome largely because of its difficult standardization.

[23] NETT Research Group: Patients at high risk of death after lung volume reduction surgery. *NEJM.* October, 2001

[24] More subjects in the medical group than in the surgical group were unable to undergo testing due to illness

[25] NETT Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. . *NEJM.* May 22, 2003.

[26] The article identifying a high-risk population had utilized a classification of heterogeneous or homogeneous distribution of emphysema from high resolution CT scans. Radiologists also classified the distribution of patients as those with upper-lobe predominant, lower-lobe predominant, diffuse, or superior segments of lower lobes predominantly involved emphysema. The latter three categories were later combined as non-upper-lobe predominant emphysema for the final subgroup analysis.

[27] National Heart, Lung, and Blood Institute and World Health Organization. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease NHLBI/WHO Workshop Report.* April 1998.

[28] Hulley et al. *Designing Clinical Research.* 2001.

[29] NETT Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *New England Journal of Medicine.* May 2003.

[30] The existence of a surgical placebo effect has been cited elsewhere. See for example: M Tonelli et al. Clinical Experimentation: Lessons from LVRS. *Chest.* 1996.

[31] Wennberg et al. Variation in carotid endarterectomy, Mortality in the Medicare population. *JAMA.* April 1998.

[32] Based on a mean follow-up of 29.2 months.

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